Clinical Pearls and Pitfalls

The clinical dilemma of "silent desensitization" in aspirin-exacerbated respiratory disease

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ABSTRACT

Aspirin desensitization is a treatment option for patients with aspirin-exacerbated respiratory disease (AERD). Some patients with an excellent history of aspirin or nonsteroidal anti-inflammatory drug (NSAID) reactions have negative aspirin challenges/desensitization. This study discusses the clinical entity of silent desensitization in AERD and the dilemma that this presents to the practicing allergist/immunologist. We discuss a series of patients with a strong history of NSAID reactions who initially underwent a negative challenge/silent desensitization. These patients were subsequently proven to have AERD after a second positive aspirin challenge. Silent desensitization is an uncommon but important outcome to recognize in AERD. Clinicians performing aspirin desensitization should understand that this can occur and consider a second confirmatory aspirin challenge in some patients.

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Question:

In a patient with nasal polyposis, asthma, and chronic sinusitis who has a history of two or more respiratory reactions to aspirin or other nonsteroidal anti-inflammatory drugs, what is the likelihood that they have aspirin-exacerbated respiratory disease?

A. 71%
B. 75%
C. 89%
D. 93%
E. 100%

The responses to oral aspirin challenges (OACs) in patients with aspirin-exacerbated respiratory disease (AERD) are influenced by bronchial hyperactivity, aspirin challenge dose, and the presence of leukotriene modifiers and antihistamines.[1–3] To maximize safety, OAC is scheduled during asthma remissions, using inhaled and sometimes systemic corticosteroids, long-acting bronchodilators, and leukotriene modifiers. Antihistamines are routinely withheld because they block upper airway reactions.[3,4] Leukotriene modifiers partially or completely prevent the lower airways response to aspirin.[1,2,5] A starting dose of 30 or 40.5 mg of aspirin is recommended.[4] If respiratory reactions occur during OAC, the diagnosis of AERD is secured. If no reaction occurs, one of two possibilities has occurred: (A) the patient does not have AERD or (B) "silent desensitization" has occurred. Silent desensitization is a completely negative OAC in a patient with AERD, likely induced by the concurrent use of a leukotriene modifier drug and subthreshold aspirin dosing. We have observed convincing cases of silent desensitization in our clinical practices and recognize this to be a difficult dilemma for allergists performing aspirin challenges in their practice. In certain situations we point out that it also has important ramifications for patient safety.

CLINICAL PRESENTATIONS DURING ATTEMPTED ASPIRIN DESENSITIZATIONS

Patient 1 is a 27-year-old man with nasal polyposis, chronic sinusitis, and asthma, who described severe asthma after ingesting two Excedrin (Novartis, New York, NY) tablets. After pretreatment with montelukast, fluticasone/salmeterol, and prednisone at 10 mg q.d., a nasal ketorolac–modified OAC (NK/OAC) was performed.[6] This challenge was completely negative. Because of the prior history of a severe reaction to aspirin, silent desensitization to aspirin was suspected and he was treated with aspirin at 325 mg b.i.d. He subsequently reported improved sense of smell, decreased nasal congestion, and no asthma activity and prednisone was decreased. Later, the patient underwent sinus surgery and was instructed by his surgeon

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to stop aspirin. Several months after surgery, he mistakenly took 440 mg of naproxen for a headache and within an hour developed status asthmaticus requiring intubation and a 3-day hospitalization. He returned for a second NK/OAC without pretreatment with montelukast or antihistamines. During this second NK challenge, he developed both a nasal ocular reaction and a 27% drop in forced expiratory volume in 1 second. He successfully completed OAC and continues aspirin at 325 mg b.i.d. at this time. His nasal and bronchial inhalers were continued but prednisone has not been needed. His previous history of reactions to Excedrin was thus shown to be accurate and our initial observed challenge was a false negative challenge, or what we have termed a "silent desensitization." The subsequent positive challenge without montelukast pretreatment indicates that this patient truly has AERD.

Patient 2 is a 62-year-old woman who presented with a 22-year history of asthma, nasal polyps, and pansinusitis, requiring four sinus operations. She ingested nonsteroidal anti-inflammatory drugs (NSAIDS) on four separate occasions and each time experienced nasal congestion, runny nose, and difficulty breathing. She underwent an OAC while taking fluticasone/salmeterol, montelukast, and a recent prednisone burst. A starting dose of 40.5 mg of aspirin was advanced every 3 hours, up to a final dose of 650 mg. Minimal rhinorrhea was observed. This could not be identified as a positive OAC and she was scheduled for a second OAC 3 weeks later. Systemic corticosteroids and montelukast were withheld for 1 week but fluticasone/salmeterol was continued. A single dose of aspirin at 650 mg was given. One hour later, audible wheezing, flushing, nasal congestion, and ear pressure occurred. The patient was treated with two nebulizer treatments, montelukast and i.v. diphenhydramine. A second dose of aspirin at 650 mg was given that afternoon without any reaction. She was discharged while continuing aspirin at 650 mg b.i.d. The patient has done well over the ensuing 4 years with return of smell, rare viral respiratory infections, and no further sinus operations.

Patient 3 is a 67-year-old woman who developed a cold that "never went away." Nasal polyps, pansinusitis, and asthma evolved. She experienced her first reaction to aspirin at 650 mg and her second to naproxen at 440 mg, both of which caused nasal congestion and an asthma attack. Her controller program consisted of montelukast and budesonide/formoterol 160/4.5 b.i.d., zileuton at 1200 mg b.i.d., and nasal mometasone. Severe and intractable nasal congestion and anosmia led her to a scheduled aspirin challenge and desensitization. NK/OAC was performed while taking the aforementioned medications and was completely negative. Nasal inspiratory flow rates remained between 100 and 110 L/min during the challenge but increased to 160 L/min directly after aspirin desensitization. The inferior turbinates decongested. She is taking aspirin at 325 mg b.i.d.; nasal membranes remain decongested and the patient's sense of smell has returned.

DIAGNOSIS

"Silent densitization" to aspirin in three patients with true AERD.

MANAGEMENT

It can be difficult to manage a nasal polyposis patient with a positive history of NSAID reactions who undergoes a negative challenge in the office. The easiest solution for the physician would be to diagnose the patient with AERD and report to the patient that they have experienced a "silent desensitization." Many times this will be correct, but some patients would ultimately be proven to not have AERD on a subsequent challenge. These patients, if they do not undergo a second challenge, will be told to take high-dose aspirin for the rest of their lives. This has implication for gastrointestinal side effects, discussion with surgeons regarding the possibilities of discontinuing aspirin before upcoming surgery, and poses a certain degree of emotional burden to the patient that they can never miss a day of aspirin therapy. Our patients should expect us to make an accurate diagnosis before determining to start a lifelong therapy.

Conversely, the patient with a negative challenge could truly have AERD. In such a patient, a bad outcome could occur if either the patient assumes that they do not have AERD or the physician concludes that they do not have AERD based on a negative challenge. This patient may then take a therapeutic dose of an NSAID and have a significant asthmatic reaction. This clearly has safety and, possibly, even medicolegal implications. A suggested diagnostic approach is outlined in Fig. 1.

The three case reports and four additional patients in Tables 1 and 2 experienced silent desensitization during their first challenges. In this series, all seven patients described prior respiratory reactions to NSAIDs. With a history of two prior NSAID respiratory reactions, the chances of having a positive OAC and, thus, AERD, is 89%, with the other 11% being either negative challenges or potential silent aspirin desensitizations.[7] Patient 1 discontinued aspirin at the request of his surgeon, did not return for redesensitization, and took naproxen at 440 mg with near fatal consequences. After his sinus surgery, he should have returned and undergone a second aspirin challenge without montelukast. Perhaps, based on the first NK/OAC, he erroneously believed that he was no longer "allergic to aspirin." In addition, because monte-

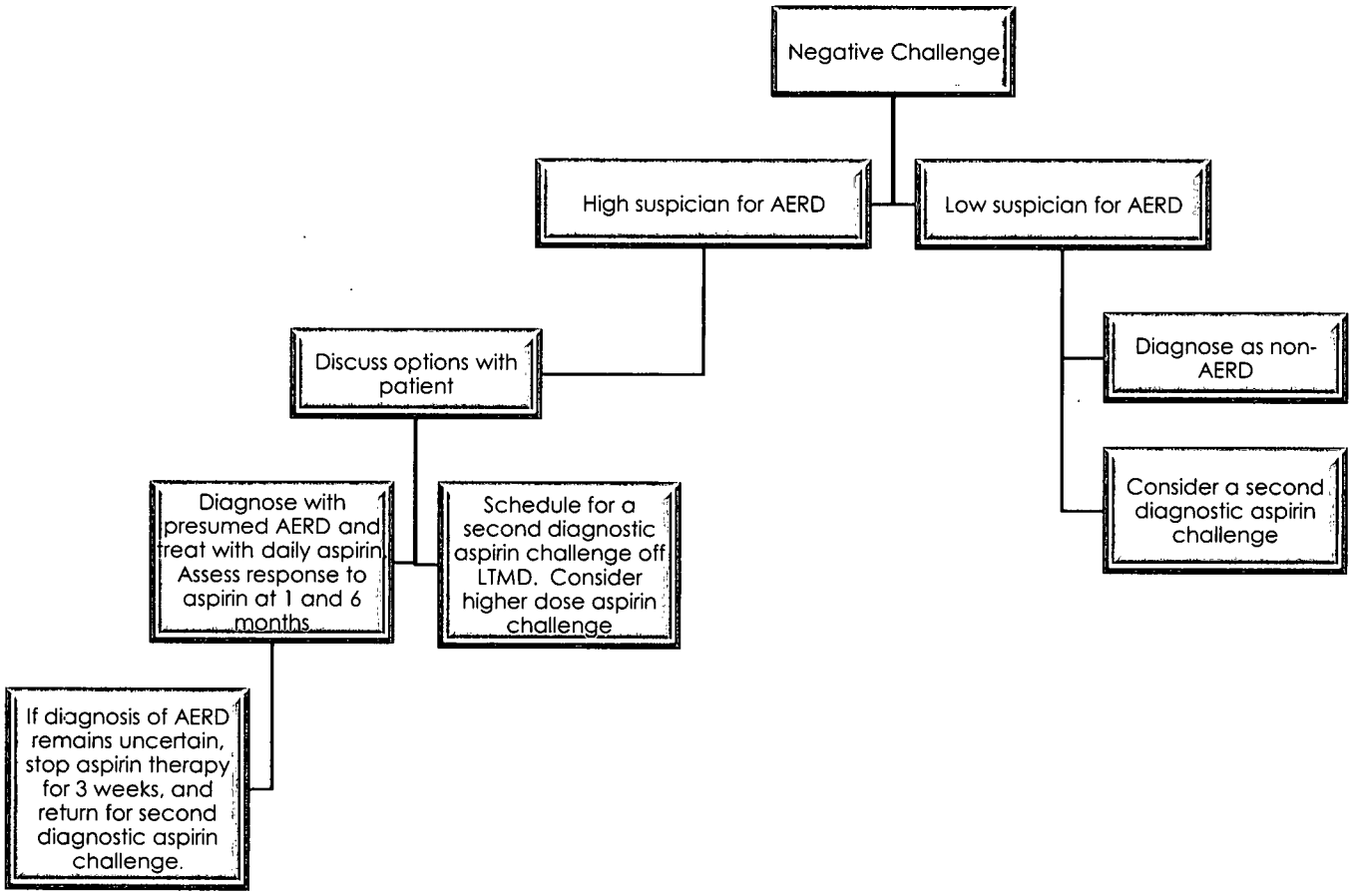

Figure 1. A suggested approach for negative challenges in suspected AERD.

lukast would have been withheld, a full challenge dose of 650 mg of aspirin, as was used in 4/6 rechallenge patients in Table 2, might have precipitated a severe asthma attack in this patient. Caution in selecting the second OAC challenge dose is encouraged and the use of NK/OAC is an alternative option.[6]

Cases 2 and 4–7 represented a recommended method of rechallenge 3 weeks or more after aspirin abstinence (Fig. 1). Leukotriene blockers, antihistamines, and systemic steroids were discontinued at least a week before the second OAC. The appropriate starting dose of aspirin for the second challenge, without montelukast and systemic corticosteroid coverage, is a difficult decision. Consideration of prior history of respiratory reactions to full doses of NSAIDs, current state of bronchial hyperirritability, and comorbidities should be used to guide the selection of a starting dose of aspirin.

Case 3 represents the patient who elected not to return for a second aspirin challenge and is the least satisfactory conclusion. Although the diagnosis of AERD can not be definitively proven, the fact that nasal decongestion occurred immediately after aspirin desensitization, the continued patency of her nasal passages over time, and the return of smell are all expected events in known AERD patients who have undergone successful aspirin desensitization and treatment with daily aspirin.

As shown in Table 3, some patients with indistinguishable histories of asthma associated with ingestion of NSAIDS will have a negative second confirmatory challenge and do not have AERD. In non-AERD, aspirin treatment provides no therapeutic benefit.

Correct answer: C, 89%

Dursen and colleagues indicated that in patients with a history of at least two reactions to NSAIDS and ongoing nasal polyps and asthma, the rate of positive oral challenges was 89%. For patients who did not take NSAIDs and only had nasal polyps with asthma, the rate was 42%. In 45 patients with severe reactions requiring hospitalization, the rechallenge rate was 100%.[7]

Pearls

- Silent desensitization to aspirin in AERD occurs and should be considered.
- A subsequent challenge (withholding Leukotriene modifier drugs, antihistamines, and oral corticoste-

Table 1 **Characteristics of seven patients undergoing challenge**

Patient No.	Age (yr)	Sex	Onset AERD (age/yr)	NSAIDs and No. of Historical Reactions	Reaction Severity	Inhaled Corticosteroids and Long-Acting Bronchodilators during Both Challenges	Systemic Steroids: First Challenge
1	27	M	23	2 Excedrin (ASA, acetaminophen, caffeine) ×1	Severe: ER	Fluticasone/salmeterol 250/50	Prednisone, 10 mg q.d.
2	62	F	40	NSAIDS ×4	Mild: Home nebulizer	Fluticasone/salmeterol 250/50	Prednisone bursts pre-OAC
3	67	F	60	ASA/Nap ×2	Mild: Home nebulizer	Budesonide/formoterol 160/4.5	None
4	38	M	23	Nap/Ibu ×2	Severe: ER	Fluticasone/salmeterol 250/50	Prednisone, 20 mg q.d. continuous
5	25	F	12	Ibu/Nap ×2	Mild: Home nebulizer	Fluticasone/salmeterol 250/50	Prednisone, 10 mg q.d. continuous
6	28	M	22	Ibu/Nap ×2	Mild: Home nebulizer	Budesonide/formoterol 160/4.5	Prednisone bursts pre-OAC
7	45	M	22	Nap/Ibu ×2	Mild: Home nebulizer	Fluticasone/salmeterol 250/50	Prednisone, 5 mg q.d.

All seven patients had pansinusitis, nasal polyps, and asthma. None were pretreated with antihistamines and all were pretreated with montelukast during the first OAC. Patients 1 and 3 underwent ketorolac nasal challenge on the first morning and modified OAC thereafter.
ER = emergency room; OAC = oral aspirin challenge; AERD = aspirin-exacerbated respiratory disease; NSAIDs = nonsteroidal anti-inflammatory drugs; ASA = aspirin; Nap = naproxen; Ibu = ibuprofen.

Table 2 **Results of the second OAC challenge**

Patient No.	Starting Challenge Dose	Provoking Dose	Nasal and Ocular Reactions	Percent Decrease in Peak Flow (L/min)	Systemic Symptoms
1	1.26 mg of NK	7.58 mg of NK	Yes	−27% FEV_1	0
2	650 mg of ASA	650 mg of ASA	Yes	15	Flushing/ear pressure
3	Not rechallenged with ASA				
4	650 mg of ASA	650 mg of ASA	Yes	20	0
5	650 mg of ASA	650 mg of ASA	Yes	10	Emesis
6	81 mg of ASA	81 mg of ASA	Yes	0	0
7	650 mg of ASA	650 mg of ASA	Yes	0	0

First pretreatment as presented in Table 1. During the second challenge, montelukast and prednisone were withheld but inhaled corticosteroids and LABA continued.
NK = nasal ketorolac; OAC = oral aspirin challenge; FEV_1 = forced expiratory volume at 1 s; ASA = aspirin.

roids for at least 1 week) should be considered in patients with a clinical history strongly consistent with AERD despite an initially negative challenge, because this could represent "silent desensitization."
- Although the mechanism of silent desensitization is not entirely clear, it likely is primarily related to the use of a leukotriene modifier drug and the typical low aspirin doses of 30–45 mg to start the challenge. Further studies are warranted to define the prevalence and other defining patient characteristics.

Pitfalls

- Some patients with AERD may experience a negative challenge/silent desensitization and be informed that they do not have AERD. If aspirin is not continued, they will be denied a therapeutic option and also be at risk for a future reaction.
- If aspirin is continued under the presumption that the patient has AERD in the face of negative challenge/silent desensitization, unless obvious and

Table 3 **Clinical characteristics of patients with histories suspicious for AERD who underwent an initial negative challenge oral aspirin challenge**

No. of Reactions to NSAIDs by History	Time Since Last Reaction	Medication(s) Inducing Reactions	Symptoms during Prior Historical Reactions	Treatment for Reactions
1	25 yr	Aspirin, 325 mg	Acute dyspnea and wheeze	β−Agonist at home
2	10 yr	Sinus tablet with aspirin	Cough, chest tightness, and dyspnea	Treated at home with MDI
3	1–20 yr	Ibuprofen, ketorolac, naproxen, 440 mg, and aspirin, 650 mg	Asthma within 30 min to all	Home treatment with Nebs and MDI
2	30 yr	Aspirin, 650 mg, and aspirin, 325 mg	"Difficulty breathing and hives on face"	Unknown
1	40 yr	Positive aspirin challenge in a research setting	Presumably asthma nasal symptoms	Unknown
1	8 yr	Aspirin, 650 mg	30 min after ingestion cough, chest and throat tightness, and facial swelling	No treatment given

All patients had adult-onset polypoid rhinosinusitis and asthma: a subsequent second challenge, with montelukast, antihistamines, and oral corticosteroids withheld, was negative confirming that these six patients did not have AERD despite a high prechallenge probability.
AERD = aspirin-exacerbated respiratory disease; NSAIDs = nonsteroidal anti-inflammatory drugs; MDI = metered-dose inhaler.

clear benefit from aspirin ensues in the coming weeks, a definitive diagnosis can not be made. This then commits the patient to a lifetime of useless, high-dose aspirin therapy.

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